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ORIGINAL RESEARCH

Efficacy and Safety of Transarterial Chemoembolization Combined with Hepatic Arterial Infusion Chemotherapy Plus Lenvatinib for Intermediate-Stage Hepatocellular Carcinoma Beyond Up-To-Seven: A Multicentre, Retrospective Propensity Score Matching Analysis

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Background: Previous LAUNCH trial revealed the promising effectiveness of transarterial chemoembolization (TACE) combined with lenvatinib for advanced hepatocellular carcinoma (HCC). However, most intermediate-stage HCC exceeds the up-to-seven criteria, limiting their potential TACE benefits. Hepatic arterial infusion chemotherapy (HAIC) was widely endorsed for delivering substantial survival benefits for high tumor burden HCC, outperforming TACE. Accordingly, we undertook this study to evaluate the efficacy and safety of TACE combined with HAIC plus lenvatinib for intermediate-stage HCC beyond up-to-seven criteria.

Methods: From June 2017 to November 2021, clinical data of intermediate-stage HCC patients beyond up-to-seven criteria received TACE combined with HAIC plus lenvatinib or TACE alone from four medical centers in China were retrospectively collected. Propensity score matching (PSM) and inverse probability weighting (IPTW) were applied to balance baseline differences. The Kaplan–Meier method was utilized for survival analysis. Cox regression-based multivariate analysis was used to identify survival-related risk factors. We compare tumor response and the incidence of adverse reactions between groups.

Results: A total of 294 intermediate-stage HCC patients beyond up-to-seven criteria received TACE combined with HAIC plus lenvatinib (the TACEHL group, n = 127) or TACE monotherapy (the TACE group, n = 167) were finally enrolled. Following propensity matching, the median OS and median PFS in the TACEHL group were 34.6 months and 15.7 months, respectively, significantly higher than the 15.7 months and 6.9 months observed in the TACE group. In tumor response, the ORR was 71.4% in the TACEHL group and 30.8% in the TACE group ($P < 0.001$), the DCR was 92.3% in the TACEHL group and 75.8% in the TACE group ($P = 0.005$). The 3–4 grade adverse reactions were comparable between the groups.

Conclusion: For intermediate-stage HCC beyond up-to-seven criteria, the integration of TACE and HAIC plus lenvatinib therapy demonstrated substantial enhancements in survival prognosis, which is a promising treatment regimen.

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Introduction

Hepatocellular carcinoma (HCC) is a remarkably heterogeneous liver malignancy and a leading cause of cancer-related mortality worldwide, ranking fourth in incidence and third in mortality.[1–3] Unfortunately, most patients present at advanced stages, precluding curative options such as surgery, ablation, or liver transplantation. Nevertheless, given the pronounced heterogeneity of HCC, its biological features including tumor diameter, count, portal vein thrombosis, and extrahepatic metastasis must be factored into the therapeutic decision-making process.[4] Intermediate-stage HCC, characterized by multiple large, multifocal tumors exceeding the up-to-seven criteria at initial diagnosis, frequently arises due to the insidious and aggressive nature of the disease. For this unique cohort, as the recognized standard treatment for intermediate-stage HCC, TACE does not confer substantial benefit, and the resulting hypoxic microenvironment can activate the VEGF pathway, fostering tumor angiogenesis and subsequent progression or recurrence.[5,6]

Lenvatinib, an efficacious multi-kinase inhibitor, exerts potent anti-neoplastic effects by inhibiting numerous pathways, most notably the vascular endothelial growth factor receptor (VEGFR). According to the REFLECT trial, lenvatinib demonstrated non-inferior efficacy to sorafenib in the treatment of unresectable HCC,[7] thereby garnering a recommendation for first-line use in BCLC stage C HCC. However, the standalone capacity of lenvatinib to manage HCC progression is limited.[8] Research indicated that the synergistic antitumor effects of combining lenvatinib with transarterial interventional therapy can be achieved, and the TACE-related hypoxic tumor microenvironment, which typically drives tumor progression, can be mitigated or even eliminated by the integration of a multi-kinase inhibitor.[9,10] The LAUNCH trial reported an impressive median overall survival of 17.8 months for advanced HCC patients treated with TACE in conjunction with lenvatinib, significantly surpassing those managed with lenvatinib monotherapy.[11] Nevertheless, the comprehensive management of large-diameter and high-burden HCC remains suboptimal with TACE-based treatments alone.

Hepatic arterial infusion chemotherapy (HAIC) is a localized chemotherapy approach that achieves precise chemotherapy of tumor lesions while circumventing the liver first-pass effect by pre-positioning microcatheters, thereby enhancing antitumor efficacy. A Phase III randomized controlled trial demonstrated that FOLFOX-HAIC for large HCC (>7.0 cm) significantly improved survival benefits compared to TACE, achieved tumor reduction and was better tolerated in terms of adverse effects.[12] Furthermore, HAIC combined with lenvatinib significantly prolonged survival while also increasing the rate of tumor surgical conversion, allowing for curative treatment and achieving long-term survival. Previously, a study had shown that drug-eluting bead TACE (DEB-TACE) combined with HAIC provided better tumor response and survival rates than DEB-TACE alone for huge HCC, particularly those with irregular margins or major vascular invasion.[13] Therefore, for intermediate stage tumors exceeding the up-to-seven criteria, TACE combined with HAIC and lenvatinib may represent a more promising therapeutic approach.

As of now, the capability of employing TACE combined with HAIC and lenvatinib for the management of intermediate-stage HCC exceeding the up-to-seven criteria remains uncharted terrain. Consequently, we conducted a retrospective, multicenter propensity score matching study aimed at elucidating the efficacy and safety of this combined approach in treating intermediate-stage HCC that surpasses the up-to-seven standards.

Materials and Methods

Study Design and Patients Characteristics

We retrospectively reviewed and screened the clinical data of intermediate-stage (BCLC stage B) HCC patients exceeding the up-to-seven criteria who underwent either TACE combined with HAIC plus lenvatinib treatment (TACEHL group) or standalone TACE (TACE group) from June 2017 to November 2021 across four medical centers in China. This multicenter, retrospective study complied with the 1975 Declaration of Helsinki and received approval

from the Ethics Committee of Shenzhen Hospital, affiliated with Huazhong University of Science and Technology. Informed consent was waived due to the retrospective nature of the study.

All included patients were diagnosed with HCC according to the criteria of the American Association for the Study of Liver Diseases (AASLD) or the European Association for the Study of the Liver (EASL), or via liver tissue pathological biopsy. The inclusion criteria were as follows: (1) age ≥18 years; (2) staging as BCLC stage B according to BCLC staging criteria; (3) exceeding the up-to-seven criteria; (4) liver function categorized as Child-Pugh A-B grade or ALBI class 1–2 grade; (5) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0; (6) adequate hematologic, with leukocyte count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<75 \times 10^9$/L, and hemoglobin <85g/L. Exclusion criteria included (1) missing clinical data; (2) follow-up duration <6 months; (3) prior treatment with other therapies before vascular therapy or lenvatinib; (4) concomitant other malignant tumors.

Treatment Procedures

All vascular interventional treatments were performed by two or more experienced interventional imaging physicians under digital subtraction angiography (DSA) guidance achieving technical success. The procedure for **hepatic arterial catheterization is as follows**: After local anesthesia of the femoral artery puncture site with 5mL of 2% lidocaine, the femoral artery was punctured successfully using the modified Seldinger technique, and a 5F vascular sheath was subsequently inserted. A 5F Yashiro catheter (Terumo, Tokyo, Japan) was passed through the sheath to successfully position in the celiac trunk artery, followed by angiography to clarify the hepatic artery course and the distribution of tumor-feeding arteries. A 2.7Fr microcatheter system (Terumo, Tokyo, Japan) was then inserted for super-selective positioning to the tumor-feeding artery.

TACE

The chemoembolization was conducted using a mixture of 20mg Epirubicin Hydrochloride (Pfizer Pharmaceutical (Wuxi) Co., Ltd.) and 10–20 mL Lipiodol (Lipiodol Ultra Fluid, Guerbet, France), administered until blood flow stagnation was observed in the target artery.

mFOLFOX6-HAIC Regimen

This included: Oxaliplatin at a dose of 85 mg/m² was given intravenously over 2 hours on day 1; Leucovorin at a dose of 400 mg/m² was administered intra-arterially over 2 hours on day 1; Fluorouracil at a dose of 400 mg/m² was given by intra-arterial injection, followed by a continuous infusion of 2400 mg/m^2 over 46 hours, all delivered through a micro-catheter. Dose adjustments were made for persistent or severe treatment-related adverse reactions, with treatment resumed once the patient condition stabilized. The TACE combined with HAIC was repeated every three weeks. Post-treatment, a full abdominal enhanced CT scan was performed every eight weeks for treatment evaluation.

Lenvatinib

Lenvatinib (Lenvima, Eisai, Tokyo, Japan) treatment was initiated within 3 days of the first TACE-HAIC treatment, with a dose of 12mg/d for patients weighing ≥60kg or 8mg/d for those weighing <60kg. If severe intolerable adverse reactions occurred, the dose was reduced to half the standard dose or temporarily suspended, with close observation and symptomatic treatment. When adverse reactions subsided or disappeared, the initial dose of the drug was gradually restored. The targeted drug was discontinued 4 days before the next TACE-HAIC cycle and resumed 3 days after. If the suspension exceeded one month, the patient was excluded from the study, with a treatment cycle of 4 weeks.

Clinical Data and Follow-Up Schedule

The comprehensive clinical data for review and collection encompass age, gender, ECOG performance status, HBV infection, cirrhosis, ascites, Child-Pugh score for liver function, ALBI score for liver function (Calculated as: log10 [Bilirubin (umol/L)] × 0.66 + Albumin (g/L) × (−0.085); Classification criteria: ALBI 1 grade: less than −2.60; ALBI 2 grade: between −2.59 and −1.39; ALBI 3 grade: over −1.39), alpha-fetoprotein (AFP) level, maximum tumor diameter, number of tumors, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin, neutrophil count, hemoglobin count, platelet count, and serum creatinine.

All enrolled patients underwent routine follow-up at 1 month post the initial treatment and subsequently every 3 months thereafter, encompassing physical examination, liver function assessment, serum alpha-fetoprotein (AFP) levels, additional biochemical blood tests and enhanced abdominal CT or MRI, chest CT, as well as any other imaging examinations deemed clinically necessary.

Survival Outcome Assessment

Overall survival (OS) was measured as the interval from the initial diagnosis of HCC to the final follow-up or clinical death. Progression-free survival (PFS) was calculated from the time of the first diagnosis of HCC to the time of disease progression as assessed by the modified Response Evaluation Criteria in Solid Tumors 1.1 (mRECIST 1.1). Tumor responses were evaluated according to the mRECIST 1.1 criteria, with assessment based on imaging data categorized as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Objective response rate (ORR) was defined as the percentage of tumor responses assessed as CR and PR. Additionally, the disease control rate (DCR) was represented as the proportion of tumor responses assessed as CR, PR, and SR. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events 5.0 (CTCAE 5.0) standard.

Propensity Score Matching and Inverse Probability of Treatment Weighting

1:1 propensity score matching (PSM) and inverse probability weighting (IPTW) were employed to balance baseline differences. The tolerance for propensity matching was set at 0.02. The covariates included in the balance were age, gender, HBV infection, cirrhosis, ascites, Child-Pugh grade, ALBI grade, alpha-fetoprotein (AFP) level, maximum tumor diameter, and tumor number.

Statistical Analysis

Statistical analysis was executed using R software (RStudio version 4.3.1) and SPSS (IBM SPSS Statistics 26, USA). Continuous variables conforming to a normal distribution are depicted as mean ± standard deviation and evaluated using Student's *t*-test. Conversely, for those not normally distributed, medians are employed and analyzed via the Mann–Whitney *U*-test. Categorical variables are expressed in terms of percentages and assessed using either the chi-square test or Fisher's exact test. Conduct survival analysis using the Kaplan–Meier method and generate Kaplan–Meier curves for OS and PFS across the entire cohort, PSM cohort and IPTW cohort. A Cox proportional hazards regression model was utilized to pinpoint independent prognostic factors affecting OS and PFS. A two-tailed P-value of less than 0.05 was deemed statistically significant.

Results

Patient Characteristics

Under rigorous qualification review, a total of 294 hCC patients met the inclusion and exclusion criteria. Among these, 127 patients underwent treatment with TACE combined with HAIC plus lenvatinib (TACEHL group), while 167 patients received solely TACE treatment (TACE group). The screening and review flow diagram is depicted in Figure 1. The overall cohort predominantly consisted of male patients (89.5%), those co-infected with HBV (89.5%), and patients with cirrhosis (91.8%). In the TACEHL group, the enrolled patients had an average age of 45.6 ± 5.2 years and a maximum tumor diameter of 9.5 ± 3.5 cm, compared to 44.6 ± 6.4 years and 8.6 ± 3.3 cm in the TACE group, respectively. Notably, a significantly higher proportion of patients in the TACE group with HBV infection, cirrhosis, ALBI grade 2, AFP levels ≤400 ng/L, maximum tumor diameters ≤7 cm and tumor number ≤3. After balancing baseline differences between the groups by propensity matching and IPTW, the aforementioned covariate discrepancies were eliminated, resulting in the IPTW cohort and the PSM cohort comprising 182 patients. The general characteristics of the enrolled patients before and after PSM are detailed in Table 1.

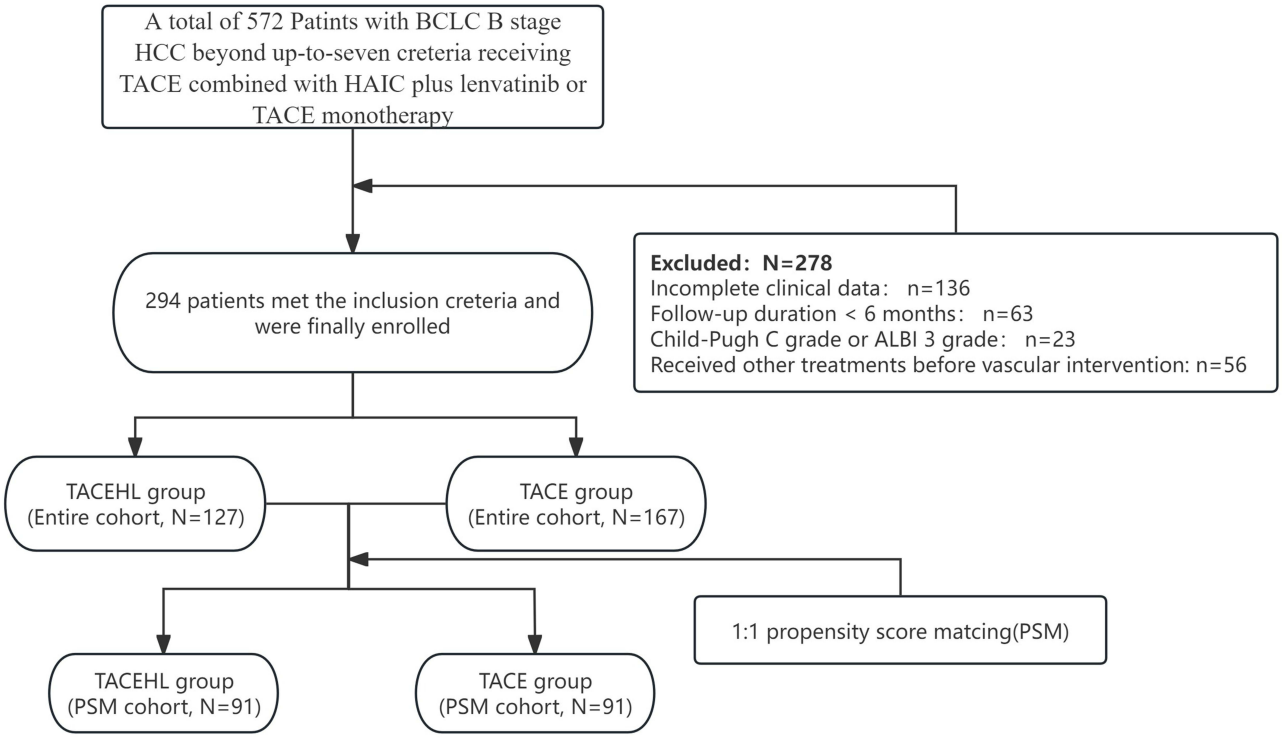

Figure 1 Flowchart of the patients selection process for this study.

Survival Outcomes

Subsequent to a median follow-up interval of 24.7 months, in the overall cohort, the combination of TACE with HAIC plus lenvatinib in patients with intermediate-stage HCC exceeding the up-to-seven criteria achieved encouraging median OS (mOS) and median PFS (mPFS) of 34.6 months (HR: 0.48; 95% CI: 0.35–0.67) and 13.3 months (HR: 0.50; 95% CI:

Table 1 Baseline Characteristics of the Study Patients Before and After PSM

	Before Matching			After Matching		
	TACEHL (n=127)	**TACE (n=167)**	**P Value**	**TACEHL (n=91)**	**TACE (n=91)**	**P Value**
Gender			0.815			0.661
Male	113(89.0%)	150(89.8%)		80(87.9%)	78(85.7%)	
Female	14(11.0%)	17(10.2%)		11(12.1%)	13(14.3%)	
Age	45.6 ± 5.2	44.6 ± 6.4	0.854	46.7 ± 5.7	45.1 ± 5.9	0.861
≤65y	100(78.7%)	130(77.8%)		70(76.9%)	69(75.8%)	
>65y	27(21.3%)	37(21.2%)		21(23.1%)	22(24.2%)	
HBsAg			0.011			0.817
Presence	107(84.3%)	156(93.4%)		80(87.9%)	81(89.0%)	
Absence	20(15.7%)	11(6.6%)		11(12.1%)	10(11.0%)	
Cirrhosis			0.002			0.203
Presence	109(85.8%)	161(96.4%)		80(87.9%)	85(93.4%)	
Absence	18(14.2%)	6(3.6%)		11(12.1%)	6(6.6%)	
Ascites			0.270			0.733
Presence	11(8.7%)	9(5.4%)		6(6.6%)	7(7.7%)	
Absence	116(91.3%)	158(94.6%)		85(93.4%)	84(92.3%)	

(*Continued*)

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Table 1 (Continued).

	Before Matching			After Matching		
	TACEHL (n=127)	**TACE (n=167)**	**P Value**	**TACEHL (n=91)**	**TACE (n=91)**	**P Value**
Child-Pugh grade			0.824			0.388
A	117(92.1%)	155(92.8%)		83(91.2%)	86(94.5%)	
B	10(7.9%)	12(7.2%)		8(8.8%)	5(5.5%)	
ALBI grade			0.024			0.643
1	85(66.9%)	90(53.9%)		60(65.9%)	57(62.6%)	
2	42(33.1%)	77(46.1%)		31(34.1%)	34(37.4%)	
AFP			0.020			0.553
≤400ng/L	58(45.7%)	99(59.3%)		50(54.9%)	46(50.5%)	
>400ng/L	69(54.3%)	68(40.7%)		41(45.1%)	45(49.5%)	
Tumor size	9.5 ± 3.5	8.6 ± 3.3	0.008	9.3 ± 3.7	9.1 ± 3.3	0.873
≤7cm	33(26.0%)	68(40.7%)		29(31.9%)	28(30.8%)	
>7cm	94(74.0%)	99(59.3%)		62(68.1%)	63(69.2%)	
Tumor number			< 0.001			0.544
2–3	87(68.5%)	71(42.5%)		53(58.2%)	57(62.6%)	
>3	40(31.5%)	96(57.5%)		38(41.9%)	34(37.4%)	
ALB (g/L), median (IQR)	46.0(38.9–53.2)	47.2(37.6–56.5)	0.511	45.5(39.7–51.2)	46.3(39.6–52.8)	0.386
ALT (U/L), median (IQR)	59.7(42.1–79.6)	61.9(40.9–83.3)	0.614	60.3(39.6–87.1)	61.7(41.7–86.9)	0.772
AST (U/L), median (IQR)	73.2(51.7–83.2)	76.1(51.1–88.6)	0.317	72.1(55.3–91.9)	76.5(53.2–93.5)	0.538
TBIL (umol/l), median (IQR)	16.1(11.3–21.9)	15.7(10.1–22.7)	0.237	16.5(12.7–19.8)	16.2(13.0–19.1)	0.419
Conversion to resection			0.003			< 0.0001
Presence	32(25.2%)	19(11.3%)		25(27.5%)	8(8.8%)	
Absence	95(74.8%)	148(88.7%)		66(725%)	82(91.2%)	

Note: P-value < 0.05 indicated a significant difference.

Abbreviations: PSM, propensity score matching; TACE, transarterial chemoembolization; TACEHL, transarterial chemoembolization combined with hepatic arterial infusion chemotherapy plus lenvatinib; HBsAg, hepatitis B surface antigen; ALBI, albumin–bilirubin ratio; AFP, α-fetoprotein; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin.

0.38–0.65), respectively, significantly superior to those of the TACE-only group at 16.6 months (HR: 2.08; 95% CI: 1.50–2.89) and 6.6 months (HR: 2.02; 95% CI: 1.53–2.66), with all P values < 0.001. The 1-year, 2-year, and 3-year OS rates and 6-month, 1-year, and 2-year PFS rates for the combination regimen of TACE plus HAIC and lenvatinib were 63.8%, 31.5%, 17.3%, and 68.5%, 48.3%, 21.3%, respectively, significantly higher than the 44.9%, 23.6%, 11.4%, and 49.7%, 21.6%, 10.2% observed in the TACE-only regimen (P < 0.001). In the PSM cohort, the mOS for the TACEHL group and TACE group were 34.6 months (HR: 0.45; 95% CI: 0.30–0.68) and 15.7 months (HR: 2.20; 95% CI: 1.46–3.32), respectively, with a P value of 0.005, and the mPFS were 15.7 months (HR: 0.44; 95% CI: 0.31–0.62) and 6.9 months (HR: 2.28; 95% CI: 1.61–3.23), respectively, with a P value of 0.02. The 1-year, 2-year, and 3-year OS rates and 6-month, 1-year, and 2-year PFS rates for the TACEHL group were 64.8%, 30.8%, 16.5%, and 65.9%, 45.2%, 19.8%, respectively, similarly significantly higher than the 48.4%, 24.2%, 13.2%, and 50.5%, 27.5%, 14.3% in the TACE group (P < 0.001). The similarly more advantageous survival benefits of TACE combined with HAIC plus lenvatinib regimen were also observed in the IPTW cohort. Kaplan–Meier curves for OS and PFS across the three cohorts are presented in Figure 2.

Tumor Response

Among the entire cohort, 17 and 7 cases achieved CR in the TACEHL and the TACE groups, respectively, 76 and 44 cases achieved PR, 25 and 68 cases reached SD, while 9 and 48 cases experienced PD. In terms of overall tumor response, the TACEHL group significantly outperformed the TACE group (P < 0.001). The TACEHL group achieved encouraging ORR and DCR of 73.2% and 92.9%, respectively, which were significantly higher than 30.5% and 71.3% in the TACE alone group

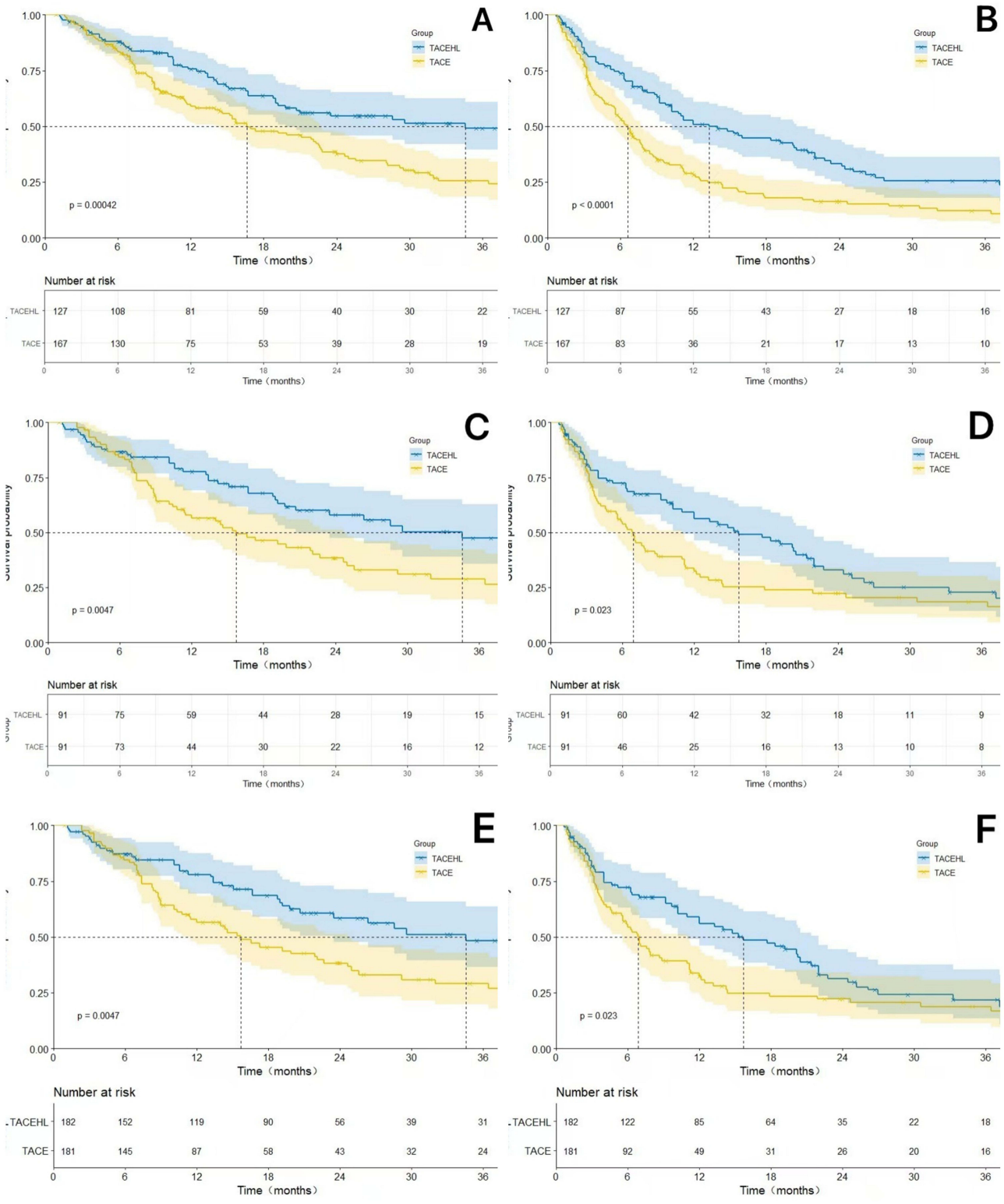

Figure 2 The Kaplan–Meier survival curves by Log rank test for the TACEHL group and the TACE group with or without propensity score matching (PSM) or inverse probability of treatment weighting (IPTW) adjustment. (**A**) The Kaplan–Meier curves comparing the overall survival between the TACEHL group and the TACE group without adjustment; (**B**) The Kaplan–Meier curves comparing the overall survival between the TACEHL group and the TACE group without adjustment; (**C**) Comparison of PSM-adjusted overall survival between the TACEHL group and TACE groups; (**D**) Comparison of PSM-adjusted progression-free survival between the TACEHL group and TACE groups. (**E**) Comparison of IPTW-adjusted overall survival between the TACEHL group and TACE groups. (**F**) Comparison of IPTW-adjusted progression-free survival between the TACEHL group and TACE groups.

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(P values < 0.001). In the PSM cohort, the TACE combined with HAIC plus lenvatinib regimen also showed superior performance in all aspects compared to the TACE monotherapy. Specifically, the ORR was 71.4% and 31.8% in the TACEHL and TACE groups, respectively (P < 0.001). The DCR was 92.3% and 75.8% in the TACEHL group and the TACE group, respectively (P = 0.005). The best tumor response before and after propensity matching adjustment is shown in Table 2. The subsequent treatment strategies for these two groups are detailed in Supplementary Table 1.

Survival Related Risk Factors and Subgroup Analysis

Univariate and multivariate analyses were conducted using the Cox proportional hazards regression model. In the univariate analysis, covariates with P > 0.1 were collectively included in the multivariable analysis. The multivariable analysis revealed that ALBI stage 2, AFP levels ≥400 ng/mL, and solitary TACE treatment were independent risk factors associated with limited OS. Conversely, AFP levels ≥400 ng/mL, tumor diameter >7 cm, tumor number >3, and solitary TACE treatment were independent risk factors associated with poor PFS. Outcomes of the univariate and multivariate analyses are presented in Table 3.

Table 2 Best Tumor Response Before and After Propensity Matching Adjustment

	Before PSM			After PSM		
	TACEHL group (n=127)	TACE group (n=167)	P value	TACEHL group (n=91)	TACE group (n=91)	P value
Best Response			< 0.001			< 0.001
CR	17(13.4)	7(4.2)		13(14.3)	2(2.2)	
PR	76(59.8)	44(26.3)		52(57.1)	26(28.6)	
SD	25(19.7)	68(40.7)		19(20.9)	41(45.1)	
PD	9(7.1)	48(28.7)		7(7.7)	22(24.2)	
ORR	73.2% (93/127)	30.5% (51/167)	< 0.001	71.4% (65/91)	30.8% (28/91)	< 0.001
DCR	92.9% (118/127)	71.3% (119/167)	< 0.001	92.3% (84/91)	75.8% (69/91)	0.005

Abbreviations: PSM, propensity score matching; TACE, transarterial chemoembolization; TACEHL, transarterial chemoembolization combined with hepatic arterial infusion chemotherapy plus lenvatinib; CR, complete response, PR, partial response, SD, stable disease, PD, progressive disease, ORR, objective response rate, DCR, disease control rate.

Table 3 Risk Factors for Overall Survival and Progression-Free Survival Based on Uni- and Multivariate Analysis

Factors	Overall Survival				Progression-Free Survival			
	Univariate Analysis	Multivariate Analysis			Univariate Analysis	Multivariate Analysis		
	P value	HR	95% CI	P value	P value	HR	95% CI	P value
Gender	0.284	-	-	-	0.820	-	-	-
Male								
Female								
Age	0.704	-	-	-	0.327	-	-	-
≤65y								
>65y								
HBsAg	0.140	-	-	-	0.274	-	-	-
Presence								
Absence								

(*Continued*)

Table 3 (Continued).

Factors	Overall Survival				Progression-Free Survival			
	Univariate Analysis	Multivariate Analysis			Univariate Analysis	Multivariate Analysis		
	P value	HR	95% CI	P value	P value	HR	95% CI	P value
Cirrhosis	0.296	-	-	-	0.364	-	-	-
Presence								
Absence								
Ascites	0.973	-	-	-	0.972	-	-	-
Presence								
Absence								
Child-Pugh grade	0.397	-	-	-	0.295	-	-	-
A								
B								
ALBI grade	**0.006**	1.42	1.03–1.97	**0.033**	**0.020**	1.26	0.95–1.67	0.105
1								
2								
AFP	**0.011**	1.73	1.26–2.38	**0.001**	**0.024**	1.58	1.19–2.07	**0.001**
≤400ng/								
>400ng/L								
Tumor size	**0.075**	1.38	0.98–1.97	0.065	**0.095**	1.36	1.01–1.83	**0.044**
≤7cm								
>7cm								
Tumor number	0.528	-	-	-	**0.001**	1.47	1.11–1.93	**0.007**
2–3								
>3								
Treatment regimen	**< 0.001**	0.49	0.35–0.69	**< 0.001**	**< 0.001**	0.54	0.40–0.73	**< 0.001**
TACEHL								
TACE								

Note: Bold indicates statistical significance level at p-value < 0.05.

Abbreviations: HR, hazard ratios; CI, confidence interval; HBsAg, hepatitis B surface antigen; ALBI, albumin–bilirubin ratio; AFP, α-fetoprotein; TACE, transarterial chemoembolization; TACEHL, transarterial chemoembolization combined with hepatic arterial infusion chemotherapy plus lenvatinib.

In the context of subgroup analysis, all subgroups, excluding the female subgroup, the subgroup without HBV infection, the subgroup without ascites, and the Child-Pugh B subgroup showing no significant differences related to the treatment regimen, exhibited significantly extended OS in the TACEHL group compared to the sole TACE group. Furthermore, no significant differences in PFS related to the treatment regimen were observed in the female subgroup and the non-cirrhotic subgroup, and the TACEHL group demonstrated significantly superior PFS compared to the TACE group in all other subgroups. The forest plot for the subgroup analysis is presented in Figure 3.

Treatment Related Adverse Events

The majority of adverse events observed were grade 1–2. The incidence rates of grade 1–2 adverse reactions were comparable between the TACEHL group and the TACE group, with no treatment-related mortalities occurring throughout the treatment process. Notably, the TACEHL group experienced 11 cases (8.9%) of neurologic toxicity, in contrast, the TACE group observed 0 cases ($P < 0.001$). The most prevalent grade 1–2 adverse reactions in the TACEHL group were abdominal pain (59.8%), fever (52.8%), and elevated AST (51.5%), and the TACE group also experienced abdominal pain (53.3%), fever (59.7%), and elevated AST (44.9%) as the most common grade 1–2 treatment related adverse reactions. Additionally, elevated AST (6.8%), elevated ALT (20.5%), and hypertension (17.3%) were the most prominent grade 3–4 treatment related adverse reactions in the TACEHL group, and the most frequent grade 3–4 adverse

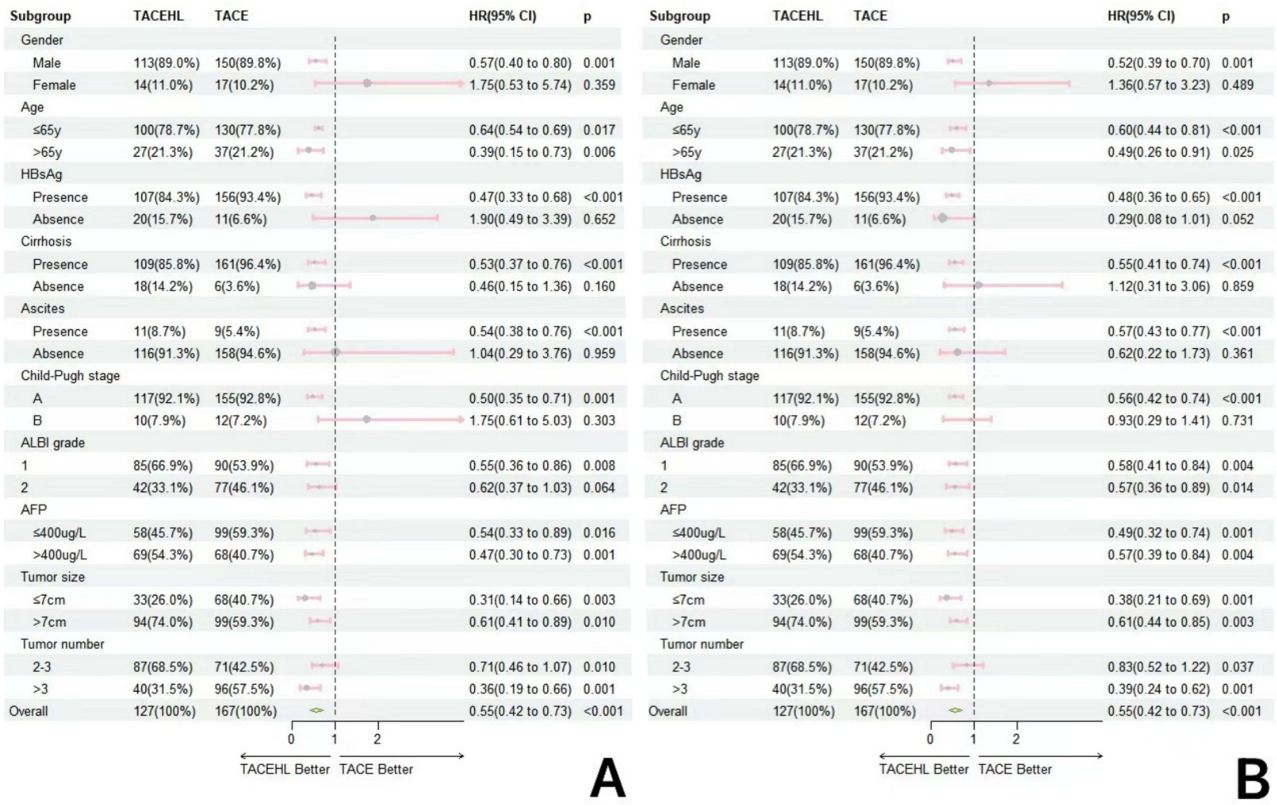

Figure 3 Forestplot based on overall survival (**A**) and progression-free survival (**B**) of each subgroup.

reactions of TACE group were elevated AST (21.0%), elevated ALT (14.4%), and abdominal pain (12.6%). Detailed information on all treatment-related adverse events is presented in Table 4.

Discussion

The present multicenter retrospective study first explored the safety and efficacy of TACE combined with HAIC and lenvatinib for the treatment of BCLC stage B HCC beyond up-to-seven criteria. The outcomes indicated that the combination of TACE, HAIC, and lenvatinib could significantly improve the survival prognosis and tolerance of patients with up-to-seven criteria BCLC stage B HCC. After PSM, the mOS and mPFS of the TACE combined with HAIC plus lenvatinib treatment regimen were 34.6 months and 15.7 months, respectively, significantly longer than the 15.7 months and 6.9 months observed in the TACE monotherapy regimen. In terms of tumor response, the TACEHL group achieved an encouraging 71.4% ORR and 91.3% DCR, with a satisfactory surgical conversion rate of 27.5%. Therefore, the combination of TACE and HAIC plus lenvatinib not only significantly improves survival but also but also demonstrates remarkable efficacy in reducing viable tumor components thereby improving opportunities for surgical conversion and effectively delaying disease progression, making it a promising approach for managing HCC with high tumor burden.

The satisfactory survival benefits observed may be attributed to several factors. Firstly, chemotherapy agents induce immunogenic cell death in tumor cells through DNA damage and apoptosis mechanisms, concurrently Lenvatinib attenuates the fibroblast growth factor receptor (FGFR) signaling pathway to reduce the differentiation of regulatory T cells and enhances natural killer cell activity,[14–16] thereby jointly improving the tumor microenvironment. Secondly, as a multi-kinase inhibitor with anti-angiogenic properties, lenvatinib inhibits tumor growth by reducing blood supply and simultaneously normalizes tumor vasculature to enhance chemotherapy efficacy and reduce tumor resistance.[17] Additionally, Lenvatinib targets the VEGFR signaling pathway driving tumor vascular proliferation and heterogeneity stimulated by the hypoxic microenvironment following TACE embolization and significantly amplifying anti-tumor

Table 4 Treatment-Related Adverse Events

Adverse Events	Grade 1/2			Grade 3/4		
	TACEHL (n=127)	TACE (n=167)	P value	TACEHL (n=127)	TACE (n=167)	P value
Hypertension	46(36.2)	52(31.1)	0.360	22(17.3)	17(10.2)	0.074
Diarrhea	44(34.6)	48(28.7)	0.280	6(4.7)	11(6.6)	0.459
Nausea/ Vomiting	39(30.7)	40(24.0)	0.195	9(7.1)	7(4.2)	0.278
Cough	16(12.6)	13(7.8)	0.170	3(2.4)	1(0.6)	0.196
Fatigue	28(22.0)	29(17.4)	0.314	1(0.8)	2(1.2)	0.729
Hematuria	13(10.2)	9(5.3)	0.118	0(0)	0(0)	1.000
Inappetence	31(24.4)	39(23.4)	0.833	3(2.4)	3(1.8)	0.734
Headache	25(19.7)	22(13.2)	0.131	2(1.6)	0(0)	0.104
Fever	67(52.8)	83(49.7)	0.604	9(7.1)	8(4.8)	0.403
Abdominal pain	76(59.8)	89(53.3)	0.262	17(13.4)	21(12.6)	0.837
Neurologic toxicity	11(8.9)	0(0)	<0.001	0(0)	0(0)	1.000
Hypothyroidism	17(13.4)	16(9.6)	0.306	0(0)	0(0)	1.000
Hyperthyroidism	22(17.3)	17(10.2)	0.107	2(1.6)	1(0.6)	0.409
Dyspnea	3(2.4)	3(1.8)	0.734	0(0)	0(0)	1.000
Rash	16(12.6)	12(7.2)	0.117	0(0)	1(0.6)	0.382
Hand-foot syndrome	21(16.5)	17(10.2)	0.108	5(3.9)	2(1.2)	0.127
Laboratory-related AEs						
Elevated ALT	59(46.5)	69(41.3)	0.379	26(20.5)	24(14.4)	0.168
Elevated AST	65(51.5)	75(44.9)	0.510	34(26.8)	35(21.0)	0.244
Gamma-glutamyltransferase increased	54(42.6)	62(37.1)	0.349	21(16.5)	19(11.4)	0.201
Anemia	36(28.3)	36(21.6)	0.180	12(9.4)	13(7.8)	0.612
Leukopenia	41(32.3)	42(25.5)	0.178	12(9.4)	9(5.3)	0.181
Neutropenia	38(29.9)	41(24.6)	0.303	9(7.1)	6(3.6)	0.177
Thrombocytopenia	43(33.9)	52(31.1)	0.621	15(11.8)	12(7.2)	0.174
Hypoalbuminemia	21(16.5)	16(9.6)	0.075	8(6.3)	8(4.8)	0.572
Hyperbilirubinemia	26(20.5)	23(13.8)	0.127	10(7.9)	11(6.6)	0.671
Elevated creatinine	19(15.0)	13(7.8)	0.158	9(7.1)	6(3.6)	0.177
Proteinuria	16(12.6)	13(7.8)	0.170	2(1.6)	3(1.8)	0.884

Note: Data represent as n (%).
Abbreviations: AEs, adverse events; TACE, transarterial chemoembolization; TACEHL, transarterial chemoembolization combined with hepatic arterial infusion chemotherapy plus lenvatinib.

impact.[18–20] Thus, lenvatinib, chemoembolization, and regional chemotherapy complement one another synergistically exerting their anticancer effects.

Previous phase III LAUNCH trial validated the efficacy of TACE combined with lenvatinib for advanced HCC with a mOS of 17.8 months and an ORR of 54.4%.[11] Recently, a retrospective study by Churen Zhou et al demonstrated that the TACE-combined-lenvatinib regimen significantly improved survival outcomes among intermediate-stage HCC patients exceeding up-to-seven criteria compared to TACE-alone treatment with an encouraging mOS of 28.0 months and an ORR of 94% notably higher than the 12.0 months and 47% observed in TACE monotherapy.[21] The relatively lower mOS in the TACE group within this study might be attributable to a higher proportion of patients with high AFP levels and significant patient attrition after propensity matching and balancing differences. Furthermore, a multicenter retrospective study by Cai, Mingyue et al reported on the use of drug-eluting bead transarterial chemoembolization (DEB-TACE) combined with HAIC and lenvatinib for large HCC with portal vein tumor thrombus showing an mOS of 16.7 months and an ORR of 61.2% lower than those observed in our analysis,[22] which mainly ascribable to the portal vein involvement population characterized by higher tumor burden and significantly worse prognosis. As HCC treatment transitions to the immunotherapy era, some scholars proposed a quadruple regimen of TACE combined with HAIC targeted therapy and immunotherapy. A recent retrospective study reported on the efficacy of this four-drug combination

in HCC patients with portal vein tumor thrombus noting an encouraging mPFS of 14.8 months and an ORR of 53.7% although the incidence of grade 3–4 adverse events has increased the regimen exhibits a certain degree of tolerability.[23]

In this study, univariate and multivariate analyses revealed that ALBI grade 2, AFP level ≥400ng/mL, maximum tumor diameter >7cm, and receipt of TACE monotherapy were risk factors associated with worse OS, while AFP level ≥400ng/mL, maximum tumor diameter >7cm, tumor number >3, and TACE-alone treatment were risk factors associated with worse PFS. Currently, impaired liver function and high-level AFP were confirmed to be associated with poor prognosis.[24–26] Among them, compared to the Child-Pugh classification, the ALBI grading standard relies on albumin and bilirubin, two factors directly tied to liver function, eliminating subjective elements within the Child-Pugh method, thereby rendering more objective and precise assessment,[27] on the other hand, the ALBI standard also demonstrated significant correlations with both OS and PFS.[28] AFP has traditionally served as a marker for reflecting the invasiveness of HCC tumors, a fact that remains unchallenged. Among the clinical variables, the maximum tumor diameter and the number of tumors are important criteria for tumor staging, indicating their significant role in the prognosis of HCC patients with high tumor burden.

In subgroup analysis, the integration regimen of TACE and HAIC plus lenvatinib demonstrated superior survival benefits compared to TACE monotherapy across the majority of subgroups. However, in the female subgroup, the HBV-uninfected subgroup, the ascitic-free subgroup, and the Child-Pugh B subgroup, comparable efficacy was observed between the TACE combined with HAIC plus lenvatinib and the TACE-alone treatment. Furthermore, no significant differences in PFS were observed in relation to the treatment regimen within the female and non-cirrhotic subgroups, with these findings largely attributed to inadequate enrollment in these subsets that induced biased comparative outcomes. Therefore, larger-scale studies are needed in the future for further validation. In terms of safety, no treatment-related death occur, elevated transaminases, abdominal pain, and hypertension are the most common Grade 3–4 adverse reactions in both the TACEHL and TACE groups. Notably, 11 cases (8.9%) in the TACEHL group experienced Grade 1–2 Neurologic toxicity, whereas none occurred in the TACE group, primarily attributed to the side effects of HAIC. The other Grade 1–2 and Grade 3–4 adverse reactions are comparable between the two groups.

There are still some limitations in this study that need to be acknowledged. First of all, due to the retrospective nature of this research, selection bias is inevitable Although PSM and IPTW were applied to balance baseline differences, inherent discrepancies remain and may potentially exert an influence. Future validation requires further random control trials for further verification. Secondly, the data for this study group come from multiple medical centers, and there may be slight differences in the procedures of vascular interventions across these centers. Additionally, the majority of the enrolled population in this study group are HBV-related HCC patients, and the applicability to HCC caused by other etiologies still needs to be further explored in large-scale international studies.

Conclusion

The combined therapeutic approach of TACE and HAIC supplemented with lenvatinib manifests excellent efficacy and acceptable safety, significantly extending the survival of patients with intermediate-stage HCC beyond seven years, concurrently achieving tumor reduction and facilitating surgical conversion, is a highly promising treatment modality.

Patient Data Confidentiality Statement

We state that all enrolled patients signed informed consent prior to treatment and all enrolled patient information enrolled in the study is treated with the utmost care and security. Access to patient data is strictly limited to authorized personnel who are required to maintain confidentiality. We employ advanced encryption technologies and robust security measures to safeguard data against unauthorized access, disclosure, alteration, or destruction. We do not share, sell, or distribute patient data to third parties without explicit consent, except as required by law or as necessary to provide the services requested by the patient. Our commitment to data confidentiality is integral to our mission, ensuring that patients can trust us with their sensitive information.

Data Sharing Statement

The data underpinning the discoveries of this study can be accessed from the corresponding author upon inquiry, in compliance with reasonable stipulations.

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The authors of this manuscript assert non-affiliation or financial association with companies whose products or services are pertinent to the subject matter discussed in the article.

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